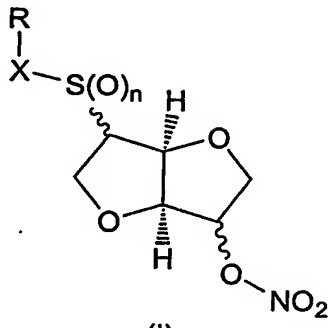
CLAIMS

1. A compound according to formula (I) or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(I)

wherein:

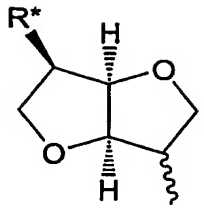
n is an integer of 0, 1, or 2,

X represents $-S(O)_m-$, $-(C=O)-$ or a single bond, wherein m is an integer of 0, 1, or 2, with the proviso that when X represents $-(C=O)-$ then n is 0,

R represents hydrogen or is a residue R^a, which residue R^a is selected from the group consisting of:

C_{1-6} alkyl;
C_{2-6} alkenyl;
C_{3-8} cycloalkyl;
C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
C_{4-8} cycloalkenyl;
C_{4-8} cycloalkenyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
phenyl;

pyridyl;
thiophenyl;
nitrosyl;
S-cysteinyl;
S-glutathionyl; and

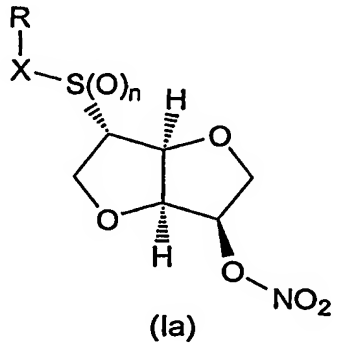


,

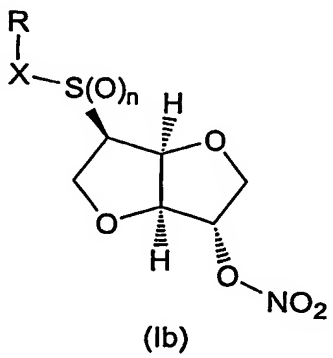
wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen;

wherein R^a optionally is substituted by one to three groups independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

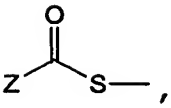
provided that when $RXS(O)_n$- and $-ONO_2$ are trans to each other with respect to the ring plane as depicted in formulae (Ia) and (Ib):



(Ia)



(Ib)

then $RXS(O)_n$- does not represent  , wherein Z is an C_1-C_4 alkyl group, aryl group, or an aralkyl group.

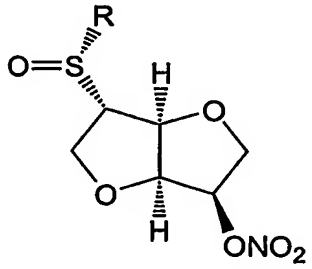
2. A compound according to claim 1, wherein either one or both of m and n is 0.

3. A compound according to any one of claims 1 to 2, wherein X represents a single bond or -S-.

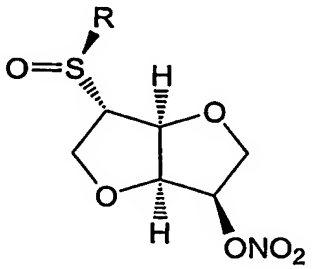
4. A compound according to any one of claims 1 to 3, wherein R represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, (C_{1-6} alkyl)C_{3-8} cycloalkyl, (C_{1-6} alkyl)C_{4-8} cycloalkenyl, phenyl, (C_{1-6} alkyl)phenyl, 5-acetyloxyisosorbid-2-yl, 5-hydroxyisosorbid-2-yl or 5-nitratoisosorbid-2-yl.

5. A compound according to any one of claims 1 to 4, wherein R is C_{1-6} alkyl.

6. A compound according to any one of claims 1 to 5, which is a compound according to formula (Ic) or (Id):



(Ic)



(Id)

7. A compound according to any one of claims 1 to 6, which is selected from:

2-thioisosorbide 5-mononitrate,
5,5′-dinitrate-2,2′-dithiodiisosorbide,

2-methylthioisosorbide 5-mononitrate,
2-[(R)-methylsulfinyl]isosorbide 5-mononitrate,
2-[(S)-methylsulfinyl]isosorbide 5-mononitrate
2-methylsulfinylisosorbide 5-mononitrate,
2-methylsulfonylisosorbide 5-mononitrate,
S-nitroso-2-thioisosorbide 5-mononitrate,
2-(tetrahydropyran-2-yl-thio)isosorbide 5-mononitrate,
2-(isosorbidyl-2'-dithio)isosorbide 5-mononitrate,
and
2-(5'-acetyloxyisosorbidyl-2'-dithio)isosorbide
5-mononitrate.

8. A pharmaceutical composition comprising as active ingredient(s) at least one compound according to any one of claims 1 to 7, optionally together with one or more physiologically acceptable excipient(s), activator(s), chelating agent(s) and/or stabilizer(s).

9. The pharmaceutical composition according to claim 8, which further comprises a thrombolytic agent, preferably a plasminogen activator, urokinase, streptokinase, alteplase or anistreplase.

10. The pharmaceutical composition according to claims 8 or 9, which further comprises an anticoagulant agent, preferably heparin, dicoumarol, acenocoumarol, enoxaparine or pentosan polysulfate.

11. The pharmaceutical composition according to any one of claims 8 to 10, which further comprises an antithrombotic agent, preferably acetylsalicylic acid, dipyridamole, ticlopidine, clopidrogel, triflusal, pentosan polysulfate or abciximab.

12. The pharmaceutical composition according to any one of claims 8 to 11, which further comprises an immunoglobulin or

a fragment thereof having a specificity for glycoprotein IIb/IIIa.

13. The pharmaceutical composition according to any one of claims 8 to 12, which further comprises an hypolipemiant agent, preferably simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, eptastatin , lifibrol, acifran, acitemate, glunicate and rosuvastatin.

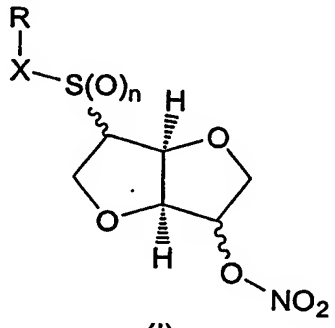
14. The pharmaceutical composition according to any one of claims 8 to 13, which further comprises an antioxidant/free radical scavenger agent, preferably nicaraven, ranolazine, emoxipin, glutatione, edaravone, raxofelast, lycopene, N-acetyl-L-cysteine, N-acetyl-D-cysteine, a racemic mixture of N-acetyl-L-cysteine and N-acetyl-D-cysteine, or carvedilol.

15. The pharmaceutical composition according to any one of the claims 8 to 14 for the prevention and/or treatment of atherosclerosis, endothelial dysfunctions, vasospasm, cardiac allograft vasculopathy, dysfunctions of the circulatory system, platelet activation, thrombosis, stroke, pathological conditions where oxidative stress plays an important role in their pathogenesis, pathological conditions where a deficit of nitric oxide plays an important role in their pathogenesis, and/or tissue damage due to ischemia and/or due to ischemia-reperfusion.

16. The pharmaceutical composition according to claim 15, wherein the pathological conditions where oxidative stress plays an important role in their pathogenesis are selected from allergies, stroke, Alzheimer's disease, and ischemic cardiovascular diseases.

17. The pharmaceutical composition according to any one of claims 8 to 14 for the treatment and/or prevention of dysfunctions of the circulatory system, preferably cardiovascular and/or coronary dysfunctions.

18. Use of at least one compound of formula (I) or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(I)

wherein:

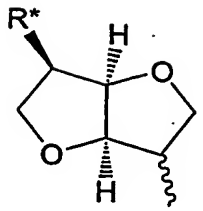
n is an integer of 0, 1, or 2,

X represents $-S(O)_m-$, $-(C=O)-$ or a single bond, wherein m is an integer of 0, 1, or 2, with the proviso that when X represents $-(C=O)-$ then n is 0,

R represents hydrogen or is a residue R^a, which residue R^a is selected from the group consisting of:

C_{1-6} alkyl;
C_{2-6} alkenyl;
C_{3-8} cycloalkyl;
C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
C_{4-8} cycloalkenyl;
C_{4-8} cycloalkenyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
phenyl;
pyridyl;
thiophenyl;
nitrosyl;

S-cysteinyl;
S-glutathionyl; and

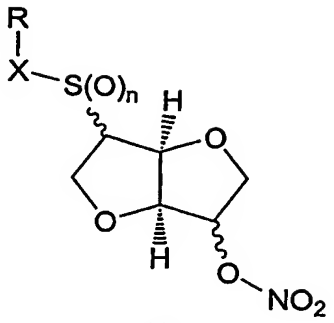


wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen;

wherein R^a optionally is substituted by one to three groups independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

as active ingredient(s) for the manufacture of a pharmaceutical composition for the prevention and/or treatment of atherosclerosis, endothelial dysfunctions, vasospasm, cardiac allograft vasculopathy, dysfunctions of the circulatory system, platelet activation, thrombosis, stroke, pathological conditions where oxidative stress plays an important role in their pathogenesis, pathological conditions where a deficit of nitric oxide plays an important role in their pathogenesis, and/or tissue damage due to ischemia and/or due to ischemia-reperfusion.

19. Use of at least one compound of formula (I):



(I)

or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof as active ingredient(s) for the prevention and/or treatment of atherosclerosis, endothelial dysfunctions, vasospasm, cardiac allograft vasculopathy, dysfunctions of the circulatory system, platelet activation, thrombosis, stroke, pathological conditions where oxidative stress plays an important role in their pathogenesis, pathological conditions where a deficit of nitric oxide plays an important role in their pathogenesis, and/or tissue damage due to ischemia and/or due to ischemia-reperfusion,

comprising administering said compound or a tautomer, pharmaceutically acceptable salt, prodrug or solvate thereof to a patient in need thereof,

wherein:

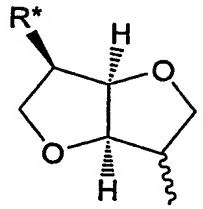
n is an integer of 0, 1, or 2,

X represents $-S(O)_m-$, $-(C=O)-$ or a single bond, wherein m is an integer of 0, 1, or 2, with the proviso that when X represents $-(C=O)-$ then n is 0,

and R represents hydrogen or is a residue R^a, which residue R^a is selected from the group consisting of:

C_{1-6} alkyl;

C_{2-6} alkenyl;
C_{3-8} cycloalkyl;
C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
C_{4-8} cycloalkenyl;
C_{4-8} cycloalkenyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
phenyl;
pyridyl;
thiophenyl;
nitrosyl;
S-cysteinyl;
S-glutathionyl; and



,

wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen;

wherein R^a optionally is substituted by one to three groups independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen.

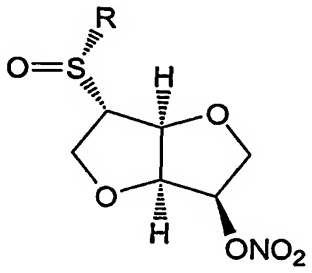
20. The use according to claims 18 or 19, wherein either one or both of m and n is 0.

21. The use according to any one of claims 18 to 20, wherein X represents a single bond or -S-.

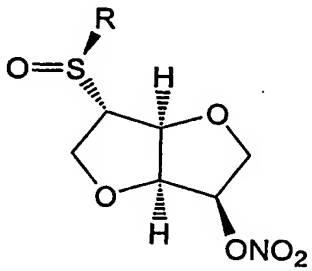
22. The use according to any one of claims 18 to 21, wherein R represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, (C_{1-6} alkyl)C_{3-8} cycloalkyl, (C_{1-6} alkyl)C_{4-8} cycloalkenyl, phenyl or (C_{1-6} alkyl)phenyl.

23. The use according to any one of claims 18 to 22, wherein R is C_{1-6} alkyl.

24. The use according to any one of claims 18 to 23, wherein the compound according to formula (I) is a compound according to formula (Ic) or (Id):



(Ic)



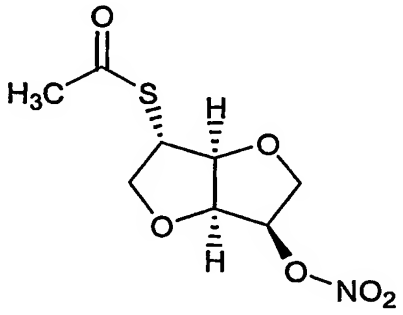
(Id)

25. The use according to any one of claims 18 to 24, wherein the compound of formula (I) is selected from:

2-thioisosorbide 5-mononitrate,
5,5'-dinitrate-2,2'-dithiodiisosorbide,
2-methylthioisosorbide 5-mononitrate,
2-[(R)-methylsulfinyl]isosorbide 5-mononitrate,
2-[(S)-methylsulfinyl]isosorbide 5-mononitrate
2-methylsulfinylisosorbide 5-mononitrate,
2-methylsulfonylisosorbide 5-mononitrate,
S-nitroso-2-thioisosorbide 5-mononitrate,
2-(tetrahydropyran-2-yl-thio)isosorbide 5-mononitrate,
2-(isosorbidyl-2'-dithio)isosorbide 5-mononitrate,
and

2-(5'-acetyloxyisosorbidyl-2'-dithio)isosorbide 5-mononitrate.

26. The use according to claim 18 or 19, wherein the compound is 2-acetylthioisosorbide 5-mononitrate, which is represented by the following formula:



27. The use according to any one of claims 18 to 26, wherein the pharmaceutical composition further comprises a thrombolytic agent, preferably a plasminogen activator, urokinase, streptokinase, alteplase or anistreplase.

28. The use according to any one of claims 18 to 27, wherein the pharmaceutical composition further comprises an anticoagulant agent, preferably heparin, dicoumarol, acenocoumarol, enoxaparine or pentosan polysulfate.

29. The use according to any one of claims 18 to 28, wherein the pharmaceutical composition further comprises an antithrombotic agent, preferably acetylsalicylic acid, dipyridamole, ticlopidine, clopidrogel, triflusal, pentosan polysulfate or abciximab.

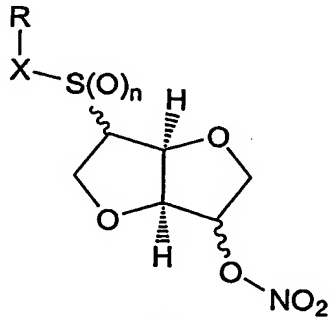
30. The use according to any one of claims 18 to 29, wherein the pharmaceutical composition further comprises an immunoglobulin or a fragment thereof having a specificity for glycoprotein IIb/IIIa.

31. The use according to any one of claims 18 to 30, wherein the pharmaceutical composition further comprises a hypolipemiant agent, preferably simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, eptastatin , lifibrol, acifran, acitemate, glunicate or rosuvastatin.

32. The use according to any one of claims 18 to 31, wherein the pharmaceutical composition further comprises an antioxidant/free radical scavenger agent, preferably nicaraven, ranolazine, emoxipin, glutatione, edaravone, raxofelast, lycopene, N-acetyl-L-cysteine, N-acetyl-D-cysteine, a racemic mixture of N-acetyl-L-cysteine and N-acetyl-D-cysteine, or carvedilol.

33. The use according to any one of claims 18 to 32, wherein the pathological conditions where oxidative stress plays an important role in their pathogenesis are selected from allergies, stroke, Alzheimer's disease, and ischemic cardiovascular diseases.

34. A process for preparing a compound of formula (I), a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(I)

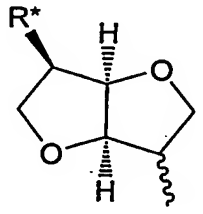
wherein:

n is an integer of 0, 1, or 2,

X represents $-S(O)_m-$ or a single bond, wherein m is an integer of 0, 1, or 2,

and R represents hydrogen or is a residue R^a, which residue R^a is selected from the group consisting of:

C_{1-6} alkyl;
C_{2-6} alkenyl;
C_{3-8} cycloalkyl;
C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
C_{4-8} cycloalkenyl;
C_{4-8} cycloalkenyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
phenyl;
pyridyl;
thiophenyl;
nitrosyl;
S-cysteinyl;
S-glutathionyl; and



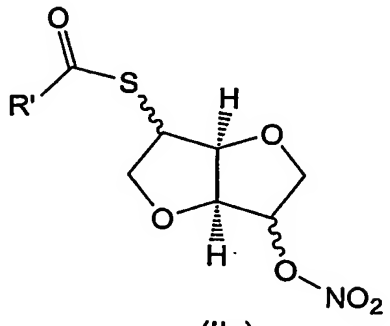
;

wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl; C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

wherein R^a optionally is substituted by one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

which process comprises conducting the following steps:

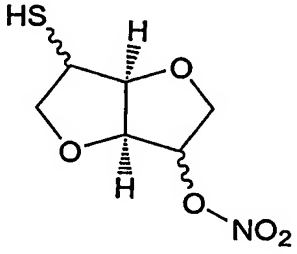
a) effecting the hydrolysis of a compound of formula (IIa):



(IIa)

wherein R' is C_1-C_6 alkyl, preferably methyl,

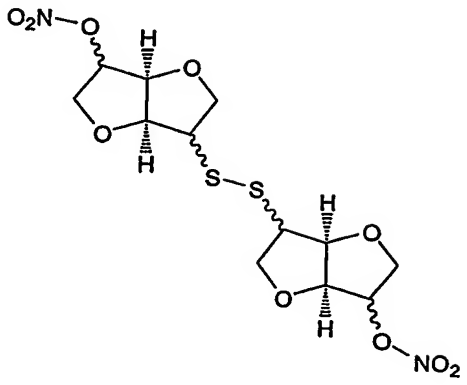
to obtain the following compound:



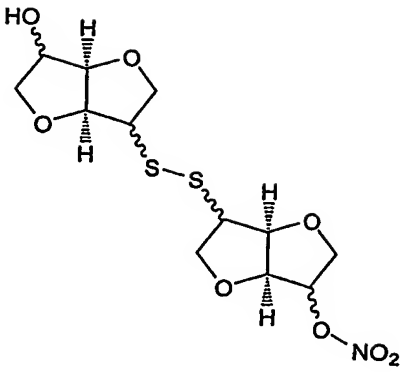
and

(b) optionally, effecting on the compound prepared according to the step (a):

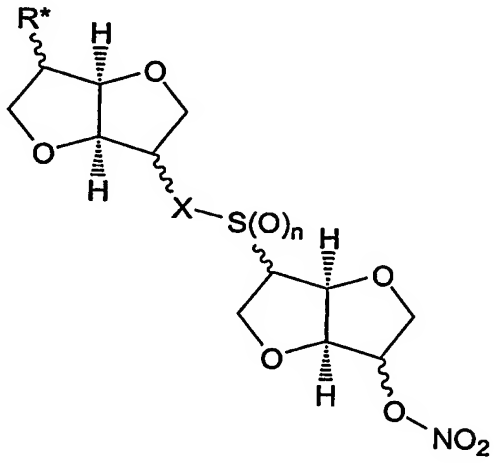
I. an oxidation reaction to obtain:



and/or



optionally followed by a second oxidation to obtain the following compound:



wherein:

n is 1 or 2,
X is $-S(O)_m-$, wherein m is 0, 1 or 2, and
R* represents hydroxyl or ONO_2;

II. a substitution reaction to obtain:

a compound according to formula (I), wherein:

n is an integer of 0,
X represents a bond,
and R does not represent nitrosyl,

optionally followed by an oxidation to obtain a compound according to formula (I), wherein:

n is an integer of 0,
X represents -S(O)m-, wherein m is an integer of 0 or 1,
and R does not represent nitrosyl;

III. a substitution reaction to obtain:

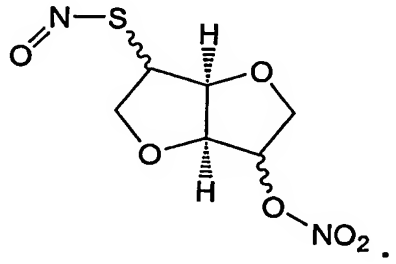
a compound according to formula (I), wherein:

n is an integer of 0, and
X represents -S-;

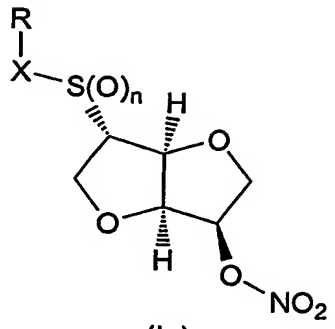
optionally followed by an oxidation to obtain a compound according to formula (I), wherein:

n is an integer of 1 or 2, and
X represents $-S(O)_m-$, wherein m is 0, 1 or 2; or

IV. a nitrosation reaction to obtain:



35. A process according to claim 34 for preparing a compound of formula (Ia), a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(Ia)

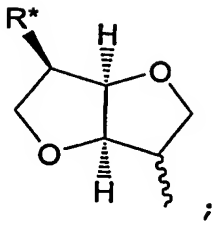
wherein:

n is an integer of 0, 1, or 2,

X represents $-S(O)_m-$ or a single bond, wherein m is an integer of 0, 1, or 2,

and R represents hydrogen or is a residue R^a, which residue R^a is selected from the group consisting of:

C_{1-6} alkyl;
C_{2-6} alkenyl;
C_{3-8} cycloalkyl;
C_{3-8} cycloalkyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
C_{4-8} cycloalkenyl;
C_{4-8} cycloalkenyl, wherein one CH_2 group is replaced by O, S, NH or NCH_3;
phenyl;
pyridyl;
thiophenyl;
nitrosyl;
S-cysteinyl;
S-glutathionyl; and



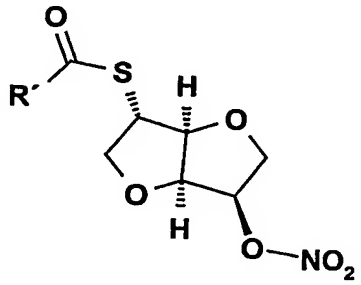
;

wherein R* is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

wherein R^a optionally is substituted by one to three groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, C_{4-8} cycloalkenyl, acetyloxy, hydroxyl, ONO_2 and halogen,

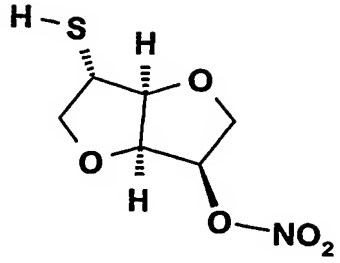
and wherein said process comprises the following steps:

(a) effecting the hydrolysis of a compound of formula (II):



(II)

wherein R′ is C_1-C_6 alkyl, preferably methyl, to obtain 2-thioisosorbide 5-mononitrate (1),



(1)

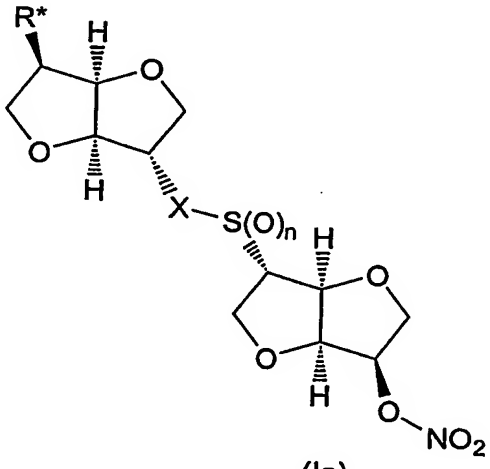
and

(b) optionally, effecting on the compound (1) prepared according to the step (a):

I. an oxidation reaction to obtain:

5,5'-dinitrato-2,2'-dithio-diisosorbide (2) or 2-(isosorbidyl-2'-dithio)-isosorbide 5-mononitrate (8),

optionally followed by a second oxidation to obtain a compound according to formula (Ie):



(Ie)

wherein:

n is 1 or 2,

X is $-S(O)_m-$, wherein m is 0, 1 or 2, and

R* represents hydroxyl or ONO_2;

II. a substitution reaction to obtain a compound according to formula (Ia), wherein:

n is an integer of 0,
X represents a bond,
and R does not represent nitrosyl,

optionally followed by an oxidation to obtain:

a compound according to formula (Ia), wherein:

n is an integer of 0,
X represents -S(O)m-, wherein m is an integer of 0 or 1,
and R does not represent nitrosyl;

III. a substitution reaction to obtain:

a compound according to formula (Ia), wherein:

n is an integer of 0, and
X represents -S-;

optionally followed by an oxidation to obtain a compound according to formula (Ia), wherein:

n is an integer of 1 or 2, and
X represents $-S(O)_m-$, wherein m is 0, 1 or 2; or

IV. a nitrosation reaction to obtain:

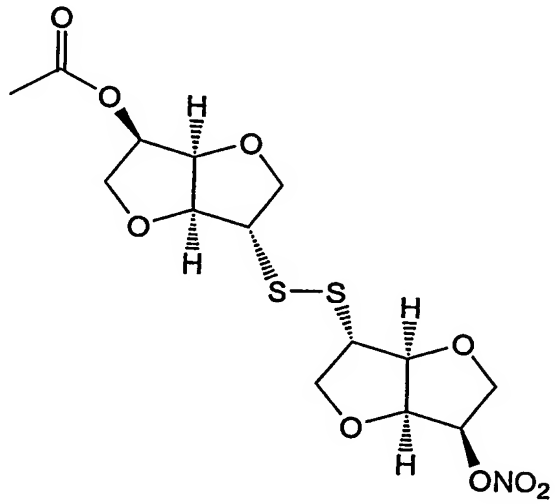
S-nitroso-2-thioisosorbide 5-mononitrate (6)

36. A process according to claim 34 or 35 that includes steps (a) and (b) II for the preparation of:

2-[(R)-methylsulfinyl]isosorbide 5-mononitrate, and/or
2-[(S)-methylsulfinyl]isosorbide 5-mononitrate.

37. A process according to claim 35, that includes the separation of both diastereoisomers.

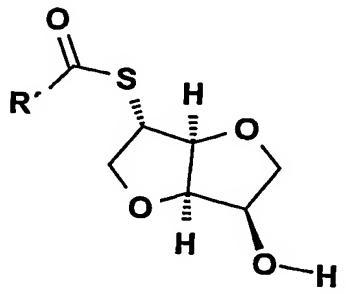
38. A process for preparing a compound of formula (11) or a tautomer, a pharmaceutically acceptable salt, a prodrug or a solvate thereof:



(11)

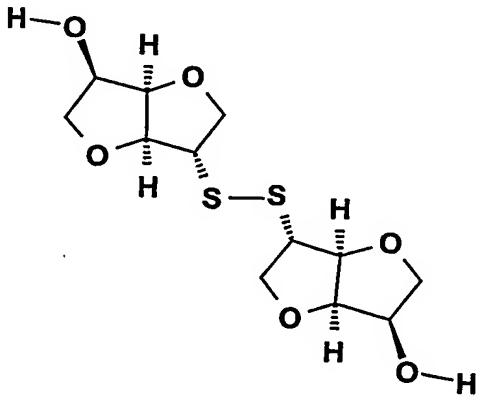
which process comprises the following steps:

a) effecting an oxidation of a compound of formula (III):



(III)

wherein R' is C_1-C_6 alkyl, preferably methyl, to obtain 2,2'-dithiodiisosorbide (10),



(10)

and

(b) effecting a nitration of the compound prepared in step (a) with a nitrating agent in the presence of a carboxylic anhydride, preferably acetic anhydride.

39. 2,2'-dithiodiisosorbide.